

REMARKS

Status of the claims:

With the above amendments, claims 1, 3-6, 8, and 10 have been amended, and claims 11 and 12 have been added. Claims 1-12 are pending and ready for further action on the merits. No new matter has been added by way of the above amendment. The amendments to the claims have support at page 6, lines 21-22, at page 5, lines 29-35, and at page 3, lines 8-25. Other amendments are simply to employ the correct transitional language. New claims 11 and 12 have support at page 6, lines 8-12 and 17-18, Examples 2-5. Reconsideration is respectfully requested in light of the following remarks.

Examiner Interview

Applicants and Applicants' representative would like to thank the Examiner for taking the time to interview with Applicants and Applicants' representative on February 12, 2004. The gist of the Interview was as follows. Applicants indicated that they would correct the 35 USC §112, second paragraph rejections simply be correcting the transitional phrase language. The rejections over 35 USC §102(b) and over 35 USC §103(a) were discussed.

Applicants insisted that the 35 USC §102(b) rejections of claims 1 and 2 were not valid rejections as the cited references

(i.e., Lebel et al. (Int. Arch. Allergy Immunol., Vol. 116, pp. 284-287, (1998) and Kessler et al. (Biochemical Pharmacology, Vol. 40, pp. 169-173, (1990)) did not teach all of the elements of claims 1 and 2. The Examiner requested a 37 CFR §1.132 declaration showing that Lebel et al. and Kessler et al. do not anticipate the instant invention. With this request, it became apparent that the Examiner meant to reject claims 1 and 2 under 35 USC §103(a) and not under 35 USC §102(b) although the Examiner did not agree with this assertion by Applicants.

The Examiner's rejection under 35 USC §112, first paragraph was also discussed.

Finally, in regard to the rejection under 35 USC §103(a), Falk '834 (US Patent No. 5,827,834) was also discussed.

Rejections under 35 USC §112, second paragraph

Claims 1-8 are rejected under 35 USC §112, second paragraph as being indefinite.

The Examiner asserts that in claims 3-6, "comprises" has been misspelled as "compromises". Applicants have amended claims 3-6 so that this has been corrected. Applicants believe that with these amendments, the rejection has been obviated. Withdrawal of the rejection is warranted and respectfully requested.

Rejections under 35 USC §102

Claims 1-2 are rejected under 3 USC §102(b) as being anticipated by Lebel et al. (*Int. Arch. Allergy Immunol.*, Vol. 116, pp. 284-287, (1998)).

Claims 1-2 are rejected under 3 USC §102(b) as being anticipated by Kessler et al. (*Biochemical Pharmacology*, Vol. 40, pp. 169-173, (1990)).

These rejections are traversed for the following reasons.

Anticipation

Section 2131 of the MPEP states: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001).

Neither Lebel et al. nor Kessler et al. can anticipate the instant invention because they simply fail to disclose the elements in the instantly claimed invention. They do not

disclose any structures or compositions, either generically or as alternatives, which fall within the scope of the claim.

First, as was argued previously in the response filed July 21, 2003, neither Lebel et al. nor Kessler et al. discloses a pharmaceutical composition as is present in the preamble of claim 1. For this reason alone, the rejection is inapposite.

Second, neither Lebel et al. nor Kessler et al. discloses cyclosporin dissolved in dimethyl sulfoxide (DMSO) wherein the concentration of cyclosporin is from 0.1% to 90% by weight of the total composition.

Failure of Lebel et al. to disclose a pharmaceutical composition

Lebel et al. disclose an *in vitro* study on dissociated nasal polyp cells in a test tube. Lebel et al. do not disclose or suggest an *in vivo* study on a whole organism, and nowhere do the authors suggest that their *in vitro* cyclosporin solution be adapted for use in animals or humans for any purpose. Thus, Lebel et al. have not produced a pharmaceutical composition that anticipates claims 1 and 2. In other words, while the Lebel et al. authors discuss the many known effects of cyclosporin on p. 286, they nowhere suggest that a cyclosporine-DMSO pharmaceutical drug be used in humans or animals.

The American Heritage Dictionary, Second Edition defines "pharmaceutical" as "Of or pertaining to pharmacy or

pharmacists" and defines "pharmacy" as "the art of preparing and dispensing drugs". Thus, it should be apparent that a pharmaceutical composition refers to a composition prepared as a drug and does not refer to an *in vitro* study on dissociated nasal polyp cells. For this reason alone, the rejection of claims 1 and 2 over Lebel et al. is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Failure of Kessler et al. to disclose a pharmaceutical composition

Kessler et al. disclose a nuclear magnetic study of cyclosporin A (CSA) in CDCl₃ (deutero chloroform) and THF-d8 (deutero tetrahydrofuran) in an effort to study the structure to elucidate information about designing new derivatives with higher activity and fewer known side effects for organ transplant graft rejection. Kessler et al. refer to CSA in DMSO at page 171, left hand column, lines 2-7 and at page 172, left hand column, lines 21-22. However, Kessler et al. say nothing of a pharmaceutical composition.

As was pointed out above, the American Heritage Dictionary, Second Edition defines "pharmaceutical" as "Of or pertaining to pharmacy or pharmacists" and defines "pharmacy" as "the art of preparing and dispensing drugs". Thus, it should be apparent that a pharmaceutical composition does not refer to a nuclear

magnetic study of cyclosporin A (CSA) in CDCl₃ (deutero chloroform) and THF-d8 (deutero tetrahydrofuran) in an effort to study the structure to elucidate information about designing new derivatives with higher activity and fewer known side effects for organ transplant graft rejection. For this reason alone, the rejection of claims 1 and 2 over Kessler et al. is inapposite.

This is further apparent when one considers that at the relatively high magnetic fields used in Kessler et al., a deuterium lock is necessary to prevent drift of the magnetic field (hence, the reason for the deutero chloroform and deutero THF). Although Kessler et al. do not explicitly state that a lock is used for the experiments of CSA in DMSO, Applicants believe that a deuterated solvent was likely used to provide this lock. This lock was likely provided by DMSO-d6 (deuterated DMSO), which is commercially available. The cost of the lowest grade DMSO-d6 (from Aldrich Catalog No. 417920) is \$72.40 for 5 milliliters. Thus, the cost for making a pharmaceutical composition using deutero DMSO is prohibitive and one of ordinary skill in the art would not use deutero DMSO in a pharmaceutical composition absent an alternative purpose. In other words, this is not a suitable pharmaceutical composition. Thus, the rejection is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Lebel et al. fail to disclose the claimed amount of cyclosporin in DMSO

Claim 1 of the instant invention recites a particular minimal concentration of cyclosporin in the pharmaceutical composition. This minimal concentration is 0.1 wt %. This element is not disclosed or remotely suggested by Lebel et al. The maximal concentration of cyclosporin Lebel et al. use in their *in vitro* study is 10 microMolar. With a molecular weight of 1202.6, one molar would be 1202.6 grams cyclosporin per liter, one milliMolar would be 1.2 grams cyclosporin per liter solution and ten microMolar would be 0.012 grams of cyclosporin per liter (or 0.012 grams cyclosporin per 1000 grams water). This means that Lebel et al. disclose 0.0012 wt% or one hundred fold less than the instantly claimed amount. For this reason alone, the rejection is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Moreover, given that a standard human daily dose of cyclosporin for immunosuppression is 5 mg/kg, or for a 70 kg person, a quantity of 350 mg per day of cyclosporin would be needed. At the Lebel et al. maximum cyclosporin concentration, one would have to administer a fluid volume of over 29 liters (6.7 gallons) a day to a person. The liquid weight of 29 liters would be over 52 lbs per day, which is not generally considered a practical or safe pharmaceutical composition, or even a

possible volume of water to be administered to a person or patient. Thus, even the maximal concentration described by Lebel et al. in their *in vitro* study cannot be considered as having disclosed a pharmaceutical composition.

For the above reasons, Applicants submit that the anticipation rejection over Lebel et al. is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Kessler et al. fail to disclose the claimed amount of cyclosporin in DMSO

Kessler et al. fail to disclose what amount of cyclosporin is present in DMSO. The Kessler et al. reference is primarily concerned with elucidating structural information about cyclosporin in CDCl_3 and THF-d8. Kessler et al. discuss cyclosporin in DMSO at page 171, left hand column, lines 1-6. However, Kessler et al. does not remotely mention what the concentration of cyclosporin is in DMSO. Concentration is not an inherent characteristic (*i.e.*, it can vary). Inherency must be a necessary result and not merely a possible result. *In re Oelrich* 666 F2d 578, 212 USPQ 323 (CCPA 1981); *Ex parte Keith et al.* 154 USPQ 320 (POBA 1966). Even if the concentration of cyclosporin in DMSO as disclosed in Kessler et al. is a possible or probable result, it is not a necessary result. Thus, the

failure to disclose the concentration cannot be used to anticipate the instant claims, which discloses a concentration of 0.1 wt% to 90 wt%. Accordingly, the rejection over Kessler et al. is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Rejections under 35 USC §103

Claims 3-10 are rejected under 35 USC §103(a) as being unpatentable over Lebel et al. taken with Falk '834 (US Patent No. 5,827,834).

This rejection is traversed for the following reasons.

Present Invention

The present invention, as recited in claim 1, relates to a pharmaceutical composition of matter in the form of a solution concentrate comprising a cyclosporin dissolved in dimethyl sulfoxide (DMSO) wherein the concentration of cyclosporin is from 0.1% to 90% by weight of the total composition.

Disclosure of Lebel et al.

Lebel et al. disclose an *in vitro* study on dissociated nasal polyp cells in a test tube. Lebel et al. discuss the many known effects of cyclosporin on page 286 of the article.

Lebel et al. do not disclose or remotely suggest an *in vivo* study on a whole organism, and nowhere do the authors suggest that their *in vitro* cyclosporin solution be adapted for use in animals or humans for any purpose. Moreover, Lebel et al. nowhere suggest that a cyclosporine-DMSO pharmaceutical drug be used in humans or animals.

Disclosure of Falk '834

Falk '834 discloses a method of treating anorectal disease which comprises applying to anorectal tissue in need of such treatment an effective amount of a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid or a pharmaceutically acceptable salt thereof in an amount of up to about 10% by weight.

Nowhere in Falk '834 is cyclosporin and DMSO used together.

Removal of the Rejection over Lebel et al. taken with Falk '834

Falk '834 discloses that hyaluronic acid makes other drugs more effective, or reduces the other drugs side effects. Please see column 10, lines 2-52. Hyaluronic acid is seen to enhance a second drug's penetration of scar tissue and other tissues improving the efficacy of that second drug. (see column 10 lines 25-30 in Falk '834). One drug (amongst a host of drugs) that hyaluronic acid is reported to enhance the penetration into

tissues is cyclosporin (column 10, line 23, column 11 lines 7 and 45, column 12, lines 13 and 51, column 13, lines 17 and 49, and column 19, line 55). Falk '834 fails to disclose ever using cyclosporin with DMSO.

Falk '834 never discloses using DMSO as a carrier, which is opposite to the instant invention wherein DMSO is used as a carrier. In this regard, Falk '834 discloses that hyaluronic acid helps DMSO enter the brain in brain tumor patients. The DMSO is reported by Falk '834 as having an enhanced therapeutic effect. This is evident when one reads column 17 lines 8-13 in Falk '834

In patients suffering from brain tumors, the swelling must be reduced. Administration of dimethyl sulfoxide (DMSO) in amounts of less than 100 gm daily in a 10% solution in hyaluronic acid (sodium hyaluronate) 300-500 mg reduces acute brain and spinal edema.

From this paragraph it should be apparent to those of ordinary skill in the art that hyaluronic acid is used to facilitate the transfer of DMSO to reduce acute brain and spinal edema. The DMSO is reported to be the active ingredient in Falk '834.

Moreover, Falk '834 is only tangentially applicable to the instantly claimed invention. While Falk '834 discloses both DMSO and cyclosporin, it is NEVER in combination together, and always in relation to co-administration with hyaluronic acid. In the one rat immunosuppression example where cyclosporin is actually

used in any experimental situation, the cyclosporin is given with hyaluronic acid and not with DMSO.

Thus, Applicants respectfully submit that one of ordinary skill in the art could not be expected to arrive at the present invention for an *in vivo* pharmaceutical formula for administration to humans by combining the Lebel et al. *in vitro* study using unpharmacologic minute doses of cyclosporin with a vanishingly small quantity of DMSO on dissociated nasal polyp cells in a test tube, together with the Falk '834 where hyaluronic acid is used separately to enhance the penetration of either DMSO or cyclosporin into tissues, but never mentions the combination of DMSO and cyclosporin TOGETHER with or without hyaluronic acid.

For the above reasons, Applicants submit that the Examiner has failed to make out a *prima facie* case of obviousness regarding the rejection over Lebel et al. taken with Falk '834. Three elements are required to make out a *prima facie* case of obviousness.

- 1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
- 2) There must be a reasonable expectation of success.

3) The prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. See MPEP §2143 and *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants submit that none of these elements are met. Neither Lebel et al. nor Falk '834 discloses or suggests a pharmaceutical composition containing both DMSO and cyclosporin. Lebel et al. fails to disclose a pharmaceutical composition as argued above and Falk '834 fails to disclose DMSO and cyclosporin together. Thus, even if Falk '834 is improperly combined with Lebel et al., one still does not arrive at the instant invention.

Moreover, the "method" claims have been amended to recite an amount of cyclosporin present in DMSO. As explained above, Lebel et al. disclose 0.012 grams cyclosporin per 1000 grams water. This means that Lebel et al. disclose 0.0012 wt% cyclosporin in the total composition or roughly one hundred fold less than the instantly claimed amount. Thus, because Falk '834 NEVER discloses cyclosporin with DMSO and Lebel et al. disclose cyclosporin in an amount outside of the claimed amount, the combination of the two references cannot arrive at the instant invention. In other words, because these two references fail to

disclose all of the elements of the instant invention, they cannot render *prima facie* obvious the instant invention.

Moreover, because neither of the references discloses a use of their compositions that is remotely close to the use claimed in the instant invention, the artisan of ordinary skill would not have the guidance necessary to arrive at the instant invention. In other words, from the disclosure of Falk '834 and Lebel et al., one of ordinary skill in the art would not expect success.

Finally, the requisite motivation for combining the references also appears to be lacking. The Lebel et al. reference is used in an *in vitro* study on nasal polyp cells. Falk '834 is used to treat anorectal disease by applying to anorectal tissue a composition comprising a pharmaceutically acceptable carrier and hyaluronic acid. Neither reference has any motivation or suggestion for combining these diverse references other than improper hindsight reconstruction. Please see *W.L. Gore & Assoc. v. Garlock, Inc.* 220 USPQ 303, 311 (Fed. Cir., 1983).

Applicants herein also submit a reference by Ran et al. (AAPS PhamSciTech 2001, 2(1): article 2) showing solvents that were studied to solubilize cyclosporin. The Introduction indicates that these are traditional solubilization approaches

to increasing the solubility of CsA. Thus, please note that DMSO is not one of the included solvents.

Further, Applicants submit a 37 CFR §1.132 declaration signed by Dr. Marcus Keep, one of the inventors of the instant invention, wherein Dr. Keep who is an expert in the medical field avers to the unobviousness of the instant invention.

For all these reasons, Applicants submit that the 35 USC §103(a) rejection over Lebel et al. taken with Falk '834 is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

Rejection under 35 USC §112, first paragraph

Claims 1-10 are rejected under 35 USC §112, first paragraph as allegedly lacking description. The Examiner asserts that the language "wherein the concentration of cyclosporin is at least 0.1% by weight of the total composition" is new matter.

Applicants have amended claim 1 to recite "wherein the concentration of cyclosporin is from 0.1% to 90% by weight of the total composition". Applicants submit that there is support for this language at page 6, lines 21-22, at page 5, lines 29-35, and at page 3, lines 8-25.

Page 6, lines 21-22 states:

The formulary drug generally contains from 0.1 to 90% if the treatment medication by weight of the total composition.

Page 5, lines 29-35 states:

The formulary drug, containing cyclosporin dissolved in DMSO, for administration into the brain and related structures, spinal cord and related structures, ventricular system and cerebrospinal fluid spaces can be manufactured and distributed containing aqueous and non-aqueous injection solutions, other pharmaceutically acceptable active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars such as mannitol to make the formulary drug isotonic, hypotonic or hypertonic with the cerebrospinal fluid; and also aqueous and non-aqueous sterile suspensions.

Page 3, lines 8-25 states:

Cyclosporins are highly lipid soluble. There are well known to the art a number of mixtures for oral and intravenous administration, usually involving a carrier solution of lipid in water emulsion, micro-emulsion or nano-emulsion or particles. For intravenous administration of this lipid in water emulsion is designed to allow administration in fluid phase mixed with salt-water solution to allow easy flow without precipitation of cyclosporin in the administering tubing or the blood. This has been acceptable in the past for simple intravenous (or oral) administration at the relatively low doses needed to treat immune rejection in transplantation or autoimmune disease.

It has recently been discovered that cyclosporin is neuroprotective when it comes into contact with neurons. Since the drugs are also systemically immunosuppressive, it would be desirable to administer them selectively into the brain or the cerebrospinal fluid around the brain. Nonsystemic local CSF administration of cyclosporin would reduce systemic immune suppression, and increase brain and spine neuron exposure compared to systemic administration, both very desirable goals in patients in need of neuroproteins but not in need of immunosuppression. Especially patients that need long term treatment neuroprotection (such as those with amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease), it is desirable to avoid the complication of, or undesirable side effect of lifelong systemic immunosuppression.

From these passages, it should be apparent that there is support for the language "wherein the concentration of cyclosporin is from 0.1% to 90% by weight of the total composition". The sentence cited on page 6, lines 21-22 provides support for an amount of 0.1% to 90% by weight of the total composition. The passage from pages 5 and 6 indicate what is meant by formulary drug and the treatment drug, respectively. From these passages, it should be apparent to those of skill in the art that support for the language in question is present.

The Examiner is also reminded that *in haec verba* support is not needed as long as one of skill in the art would recognize that there is written description support. Please see *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gosteli*, 872 F.2d 1008, 1012 10 USPQ2d 1614 (Fed. Cir. 1989) and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 39 USPQ2d 1895 (Fed. Cir. 1996).

Accordingly, Applicants submit that a new matter rejection is inapposite. Withdrawal of the rejection is warranted and respectfully requested.

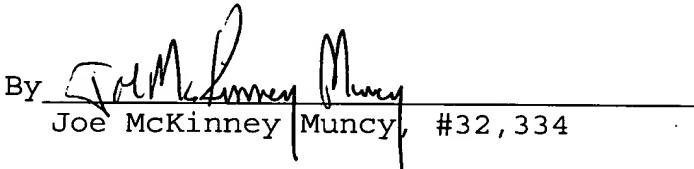
With the above remarks and amendments, Applicants believe that the claims, as they now stand, define patentable subject matter such that a passage of the instant invention to allowance is warranted. A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, T. Benjamin Schroeder (Reg. No. 50,990), in the Washington metropolitan area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Declaration under 37 C.F.R. § 1.132
Ran et al. (AAPS PhamSciTech 2001, 2(1): article 2)